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Case Report **OPEN ACCESS**

Recurrent hypoglycemia in a patient with hepatocellular carcinoma

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ABSTRACT

Hypoglycemia is a common complication of diabetes mellitus. Patients may present with any kind of symptoms, either autonomic or neuroglycopenic. Here, we report a case of a 70-year-old man with type 2 diabetes mellitus with a newly diagnosed hepatocellular carcinoma presenting with recurrent episodes of hypoglycemia. The insulin treatment was withheld initially. However, the patient's diabetic control worsened after starting treatment for his hepatocellular carcinoma. Hence, the insulin treatment was resumed. This case highlighted the challenge in balancing the management of hypoglycaemia and poor diabetic control in a patient who has diabetes mellitus and hepatocellular carcinoma. Primary care practitioners need to have high clinical suspicion to monitor these patients to prevent hypoglycemia and manage them accordingly.

Keywords: hypoglycemia, hepatocellular carcinoma, diabetes mellitus

INTRODUCTION

Hypoglycemia refers to either low plasma glucose concentration below 3.9 mmol/L, presence of autonomic or neuroglycopenic symptoms, or reversal after carbohydrate intake. Whipple's triad, which includes hypoglycaemic symptoms, a recorded low blood glucose concentration at presentation, and the alleviation of symptoms following treatment with oral or intravenous glucose, has been used to define hypoglycemia [1].

This case report aims to shed light on the recurring hypoglycemia that a patient with type II diabetes and hepatocellular cancer experienced in a primary care setting. Early diagnosis of hypoglycemia is crucial to enable proper therapy and the avoidance of catastrophic complications.

CASE PRESENTATION

A 70-year-old patient presented at an outpatient clinic complaining of sweatiness and palpitation, which started in the morning. His oral intake was the same as before. Otherwise, there were no additional symptoms of infection, hyperthyroidism, or angina. He took his regular subcutaneous insulatard 8 units the previous night but has omitted the pre-breakfast insulin this morning.

Further history revealed that he was diagnosed with diabetes mellitus three years ago, in 2019. He was previously on insulatard 8 units, premeal actrapid 6 unit three times daily and metformin XR 1 gram daily. He started experiencing several episodes of hypoglycemia at home in the past year, with his self-monitoring blood glucose ranging between 3-5 mmol/L. Among these episodes of hypoglycaemia, he had one episode of severe hypoglycemia requiring emergency treatment with an infusion of intravenous dextrose 50% which he received at a different hospital. Since then, he has reduced the insulin requirement from basal bolus insulin to twice daily, including subcutaneous insulatard 8 unit at bedtime and actrapid 8 unit pre-breakfast. While on twice insulin regime daily, his self-monitoring blood glucose was still less than 5mmol/L but he denied any symptoms of hypoglycaemia. He did not seek medical advice because of the movement restriction order (MCO).

Complicating this problem, he was accidentally found to have multiple liver lesions on ultrasound eight months ago (**Figure 1**). He was later diagnosed with chronic hepatitis B infection and was started on tablet lamivudine 100 mg OD by the gastroenterology team. A CT scan of the liver later revealed hepatocellular carcinoma with liver cirrhosis (**Figure 2**). He was decided for transarterial chemoembolization (TACE) as he refused tumor resection. The repeat CT scan showed minimal response to treatment (**Figure 3**). Hence, he was planned for a third TACE. However, the patient refused further intervention in view of the undesirable side effect of the treatment. **Table 1** shows his serial blood investigation result.

On physical examination, he was lethargic and cachectic (BMI 15kg/m2) with mild dehydration. His blood pressure was 90/60 mmHg and his pulse rate of 88 bpm. Examination of the abdomen revealed normal findings, with no stigmata of chronic liver disease. His cardiovascular and respiratory findings were within normal limits.

His capillary blood sugar was 2.7 mmol/L and he was immediately given half a cup of fruit juice and the repeat capillary blood sugar was 3.0 mmol/L. He was discharged with advice regarding hypoglycemia symptoms and management. The insulin therapy was withheld in view of symptomatic

Figure 1. Ultrasonography of abdomen (reprinted with permission of the patient)

Figure 2. Computed Tomography liver 4 phase showing multicentric hepatocellular carcinoma with liver cirrhosis (reprinted with permission of the patient)

Figure 3. Computed Tomography liver 4 phase showing multicentric hepatocellular carcinoma post-TACE with increasing size of liver lesion suggestive of disease progression (reprinted with permission of the patient)

hypoglycemia and he was maintained on Metformin XR 1 gm OD only.

After three months without receiving insulin therapy, a checkup in the outpatient clinic revealed that there had been no hypoglycemic episode; however, the patient's fasting blood sugar level was 12 mmol/L and the HbA1c was 8.0 %. The range of his self-monitoring blood glucose was 10 to 20 mmol/L. The decision was made to resume him on the basal-bolus insulin with actrapid 12 unit three times daily and subcutaneous insulatard 8 unit at bedtime. He was given closer clinic follow-up and strict advice to adjust the insulin requirement as needed. On follow-up, he had no hypoglycemia symptoms and his self-monitoring blood glucose ranged between 5 to 7mmol/L and his HbA1c was 7.9%. After discussion with the patient, a decision was made to withhold the premeal insulin and just maintain him on bedtime subcutaneous insulatard 8 unit and tablet Metformin XR 1gm ON. The decision was made in view of the status of his hepatocellular carcinoma, which was expected to progress due to a lack of active treatment. This will pose a further risk for him to develop hypoglycaemia.

Table 1. Series of laboratory findings

Laboratory parameter (Normal value)	December 2019	May 2021	March 2022	June 2022
Serum bilirubin, umol/L (3.4-17.1)	14	14	11	14
AST, U/L (5-34)	43	45	20	59
ALT, U/L (<45)	42	52	16	50
ALP, U/L (53-128)	290	148	100	199
Albumin, g/L (38-44)	41	47	37	45
Total calcium, mmol/L (2.15-2.55)	2.43	2.0	2.22	2.38
Hemoglobin, g/dl (13.5-17.4)	12.8			
HBsAg	Reactive			
HBeAg	Not reactive			
Anti-HBe	Reactive			
Anti-HCV	Not reactive			
HBV DNA, IU/ml	10342			
HIV	Not reactive			
Syphilis	Not reactive			
Serum AFP, ng/ml	5.36			
HbA1c, %	13.8	5.7	8.0	7.9

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate aminotransferase

DISCUSSION

Managing patients with diabetes and hepatocellular cancer can be very challenging for healthcare providers. Hypoglycemia is a common condition complicating patients with hepatocellular carcinoma, especially those already at risk of hypoglycaemia. There are two mechanisms of how hepatocellular carcinoma can cause hypoglycemia. The first mechanism is due to hepatocellular insufficiency. Liver cell damage caused by hepatocellular carcinoma leads to the instability of blood glucose concentration due to the disruption of the process of glycogenolysis and gluconeogenesis. Hence, hypoglycemia is quite a common presentation in patients with liver cirrhosis and is one of the prognostic factors determining mortality, especially in those with underlying hepatocellular carcinoma [1].

The second mechanism is related to paraneoplastic syndrome or known as non-islet-cell tumor hypoglycemia (NICTH). The diagnosis of non-islet-cell tumor hypoglycemia can be made in the presence of hypoglycemia and evidenced by laboratory findings of low insulin and C-peptide level, with the elevation of the ratio of IGF-2 to IGF-1 [2]. Hepatocellular carcinoma has been reported to have an association with NICTH and cause serious complications. In a few cases, patients with hepatocellular carcinoma presented with resistant hypoglycemia and required treatment with prednisolone, glucagon infusion, and even growth hormone, and subsequently died [3, 4].

The risk factor for recurrent hypoglycemia includes overly strict glycemic control, denial of the symptoms, and limited knowledge about the treatment of hypoglycemia or any concomitant drugs like beta-blocker [5]. Our patient was initially treated with subcutaneous basal-bolus insulin and was very adherent to the medication. Despite the low blood sugar level, he continued injecting himself, resulting in recurrent episodes of hypoglycemia.

An elderly patient is at an additional risk of hypoglycaemia due to the reduction in functions of the renal, hepatic, and beta-adrenergic, which can interfere with the metabolism of medication such as insulin. They also have a higher risk for common geriatric problems like instability, incontinence, immobility, or impaired consciousness which may complicate episodes of hypoglycemia [6].

There have been other reported cases with a similar presentation as our patient. In Taiwan, a young adult female reported losing consciousness and persistent hypoglycemia, requiring prednisolone therapy. A diagnosis of NICTH was obtained, and abdominal computer tomography revealed hepatocellular carcinoma with local metastases [7]. Another patient with underlying chronic Hepatitis C and liver cirrhosis who had completed antiviral therapy arrived with impaired mental status and hypoglycemia and hepatocellular cancer was also detected [8]. In unresectable hepatocellular carcinoma cases, combining a high carbohydrate diet with prednisolone and somatostatin analogue was beneficial in preventing symptomatic hypoglycemia [9].

The potential of transitory hyperglycemia brought on by cancer treatments like chemotherapy and corticosteroids poses another difficulty in managing diabetes in those with concomitant hepatocellular carcinoma [10]. In our patient, his HbA1c increased from 5.9% to 8.0% after withholding the insulin therapy and during his treatment with TACE. This causes a dilemma for the practicing doctor in determining the best course of management for this patient. However, a case of worsening hypoglycemia following TACE treatment was also reported, necessitating dextrose infusion. His condition improved following a liver transplant [11].

In cancer patients with diabetes, the glucose target should be personalised, considering the patient's life expectancy and comorbidities. In a patient with short life expectancy, the priority is to avoid the complications of hypoglycemia, acute hyperglycemia or recurrent infection that can reduce the patient's quality of life [12]. The goal to prevent diabetic-related macrovascular and microvascular complications might not be as important in those with life-limiting diagnoses such as cancer. HbA1c between 8-9% and glycemic values between 7 to 15 mmol/L are reasonable in this kind of patient [13].

HbA1c can sometimes be misleading as an indicator of diabetic control in patients undergoing cancer treatment. It can be useful as a monitoring test for pre-existing diabetes mellitus in cancer patients, but the capillary glucose testing, including fasting and post-prandial, may be more important to determine the asymptomatic hypoglycemia and acute hyperglycemia induced by corticosteroid therapy. Therefore, in cancer patients with diabetes mellitus, glycemic target and treatment may be better defined by self-monitoring blood glucose levels rather than HbA1c alone [14].

Currently, there are no specific recommendations regarding the best diabetic medication to use for patients with a concurrent diagnosis of cancer. The selection of medication should be based on the patient's comorbidities, their side effects and the potential interactions with the anticancer treatment. However, short-acting insulin analogue (lispro, asprart, glulisine) is more preferred for the management of postprandial hyperglycemia in cancer patients [14].

Metformin has also been shown to positively affect cancer patients with diabetes. Systematic review and meta-analyses report that metformin can reduce cancer mortality and cancer occurrence compared to other glucose-lowering drugs [15]. This was supported by an observational study that showed that metformin negates the development of ovarian, colorectal, prostate, liver, and other cancers [16]. Another group of oral anti-diabetic agents that also showed promising use in cancer patients is sodium-glucose transporter-2 inhibitors (SGLT-2). SGLT-2 inhibitor has also been shown to have benefits in treating patients with diabetes with cancer by inhibiting the proliferation of cancer cells [17]. Primary care physicians may consider using these medications in patients with diabetes with concurrent cancer.

CONCLUSION

Patients with diabetes and hepatocellular carcinoma are at an increased risk of developing hypoglycaemia. Primary care doctors should be more vigilant and need to evaluate these patients carefully. A personalized approach is a cornerstone in managing diabetes patients with underlying cancer taking into consideration the efficacy, tolerability and adverse effects of each treatment.

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